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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/258,132	02/26/1999	PHILIP GOELET	04990.0007.U	3407

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/258,132	GOELET ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64 and 66-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64 and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/9/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 9, 2007. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 64 and 66-71 are pending and have been examined herein.

Maintained Rejections

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 64, 66, 67, and 69-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in

the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO) 90/11372, October 4, 1990; cited in the IDS).

It is noted that EP 0412883A1 claims priority to application 8910802, which issued as and is identical in content to FR 2,650,840. An English translation of FR 2,650,840 was filed in the IDS of June 8, 1999.

Cohen teaches a method for determining the identity of one or more nucleotide bases in a nucleic acid molecule wherein the method comprises contacting a single-stranded nucleic acid sample with an oligonucleotide primer to form a duplex between the primer and complementary target nucleic acids present in the sample, wherein the primer hybridizes immediately 3' of the nucleotide to be determined; contacting the duplexes with a solution containing four different terminators, each terminator labeled with a different detectable moiety; extending the primer with the terminator, and determining the identity of the incorporated terminator to thereby determine the identity of the nucleotide base (see pages 4 and 5). Cohen (page 6) states that "if the four blocking bases are marked by means of different markers, the four blocking nucleotides are advantageously detected at the same time." In the method of Cohen, only terminator nucleotides are present in the extension reaction – the reaction does not contain dATP, dCTP, dGTP or dTTP (see, for instance, Example 1). Cohen does not teach performing the primer extension reaction using multiple primers, each comprising a different affinity moiety.

However, Davis teaches a method for determining the identity of one or more nucleotide bases in a nucleic acid molecule wherein the method comprises contacting a

single stranded nucleic acid molecule with an oligonucleotide primer to form a duplex between the primer and complementary target nucleic acids; contacting the duplexes with a solution containing labeled dNTPs, labeled with a different detectable moiety; extending the primer with the dNTPs such that if the primer is perfectly complementary with the target nucleic acid, an extension product is formed, but if the primer contains a mismatch at or near the 3' end of the primer, an extension product is not formed, and detecting the presence of an extension product in order to determine the identity of a nucleotide base (see pages 3-4). Davis teaches that the identity of multiple nucleotides can be determined simultaneously by using a mixture of different oligonucleotides, each oligonucleotide comprising a unique tail (i.e., affinity moiety). Following the extension reaction, the primer extension/target nucleic acid complex is denatured, and the primer extension product is hybridized to a solid support having bound thereto sequences complementary to the primer tail. The unique tail allows for the primers to be immobilized at specific locations on the support (see pages 4-5). Davis teaches that the use of multiple primers, with different tail sequences allows for the simultaneous analysis of multiple sequences and improves the speed and sensitivity of the detection method (see page 21).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have used multiple primers, each having a different tail (i.e., each comprising a different affinity moiety) and to have separated the primer extension products from the reaction medium by contacting the extension products with a solid support having immobilized thereon a

capture probe complementary to the tail sequence (i.e., an affinity group complementary to the affinity moiety of the primer) in order to have accomplished the objectives set forth by Davis of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

With respect to claim 66, Cohen teaches that the terminator (or "blocking nucleotide") is a dideoxynucleotide (see page 5). With respect to claim 67, Cohen teaches that the terminator comprises one or more of ddATP, ddCTP, ddGTP or ddTTP (see pages 7 and 8). With respect to claims 69 and 70, Cohen teaches that the terminator may be labeled with a fluorophore, or chromophore, isotope, enzyme or antibody (see page 5).

RESPONSE TO ARGUMENTS:

In the response, Applicants traversed this rejection by stating that the Cohen reference would have led persons skilled in the art away from any technique that required the immobilization of a nucleic acid onto a membrane. Applicants assert that Cohen teaches away from detecting immobilized nucleic acids using long-probes and short-probes. It is asserted that one of ordinary skill in the art would recognize that the long-probe technique refers to that disclosed by Stryer. A copy of page 169 of the "Stryer textbook" is provided which Applicant asserts teaches detection of a single nucleotide polymorphism by digesting DNA with a restriction enzyme and detecting the sizes of the restriction digested DNA using a long-probe. Applicants point to the teaches of Cohen at page 2 line 19 through page 3 line 17 as teaching the disadvantages of the short-probe and long-probe techniques to detect a mutation involving a single base. The

response points to Cohen as stating that the temperature conditions of Southern blotting are difficult to master to achieve suitable hybridization. The response also points to the teachings of Davis in which an oligonucleotide is spotted onto a substrate. It is argued that because Davis teaches a method in which an oligonucleotide is immobilized onto a substrate, one of ordinary skill in the art would not combine the method of Cohen with Davis since the method of Davis entails a feature that Cohen teaches is a disadvantage.

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection for the following reasons.

First, it is again acknowledged that Cohen (page 3) teaches that "By selecting suitable hybridization and rinsing conditions (specific for each system), hybridization by means of marked oligonucleotides can be achieved only in case of perfect equivalence (the difference of a single nucleotide, particularly at the site of the mutation, results in destabilization of the hybridization). However, these various techniques all have a certain number of disadvantages: - the temperature conditions are difficult to master to achieve suitable hybridization; - the mandatory presence of a restriction site may be required; - the nucleic acid is immobilized on a membrane (Southern blot) " (emphasis added). Accordingly, it is acknowledged that Cohen teaches away from using hybridization techniques to directly detect a single nucleotide mutation. Cohen teaches away from using this methodology in which hybridization of a probe to a target nucleic acid is performed to directly detect a single nucleotide variation in the target nucleic acid because the conditions of hybridization are critical to the accuracy of the assay. Immobilization of the target nucleic acid to a solid support is known to interfere to some

degree with the kinetics of the hybridization process and thereby with the specificity of hybridization. Again, the criticality of the hybridization process is important here because it is the hybridization step alone which is relied upon solely to distinguish between nucleic acids having the single nucleotide mutation from nucleic acids that do not have the single nucleotide mutation.

However, there are no teachings in Cohen which make a general conclusion that all methods of immobilizing a nucleic acid and/or all methods of hybridization should be avoided. Cohen teaches only the disadvantages of using immobilized nucleic acids to directly detect a point mutation by hybridizing a probe to the nucleic acid wherein it is the hybridization step itself detects the point mutation. All of the teachings of Cohen regarding the disadvantages of immobilized nucleic acids are limited to only methods in which hybridization with the short-probe or long-probe serves to directly detect the presence of a point mutation. Cohen does not teach away from using immobilized nucleic acids for other purposes.

Regarding Applicants statement at page 13 of the response that Cohen teaches that the long-probe Southern-blot technique has the disadvantage that the "temperature conditions are difficult to master to achieve suitable hybridization," this statement is taken out of context. The statement of Cohen regarding temperature conditions is made with respect to methods "to detect a mutation involving a single base" (page 2 of Cohen). Thus, Cohen states that the temperature conditions are difficult to master when one is trying to employ the technique to detect a specific target nucleic acid having a point mutation and to distinguish this target nucleic acid from other nucleic acids that do

not have the point mutation. Cohen does not teach that all methods of Southern hybridization are difficult to employ because of the requirement to select suitable hybridization conditions. In fact, Cohen does not specifically state that in methods of Southern hybridization, the temperature conditions are difficult to select. Rather, regarding the temperature of hybridization, Cohen only specifically states that suitable hybridization conditions must be chosen when using a short probe that distinguishes between nucleic acids having the point mutation and nucleic acids that do not have the point mutation. Contrary to the teachings of Cohen, in the method of Davis, hybridization occurs between an affinity tail and a fully complementary immobilized capture nucleic acid – i.e., not between nucleic acids that must be distinguished from one another based on the presence of a single point mutation present in the center of the short nucleotide probe. Given the teachings of Davis, the ordinary artisan would have considered it to be well within the skill of the art to select suitable hybridization conditions to hybridize the tail to a complementary immobilized capture probe. Further, Cohen teaches that the long-probes used in the method of Southern are generally over 150 nucleotides. However, in the method of Davis, the tail portion is 14 nucleotides in length and the complementary oligonucleotide is a polymer that consists of repeating units of 14 nucleotides. As stated by Davis (page 22), "The use of such repeating units of complementation favorably affects the kinetics of hybridization, further increasing the speed and the sensitivity of the assay." Thereby, it is maintained that one of ordinary skill in the art would have considered that it was well within the skill of the art to select suitable hybridization conditions for hybridizing and immobilizing the tail, since Davis

specifically provides the guidance for performing such a step. Moreover, Davis (page 21) teaches numerous advantages of including this additional step of immobilizing the tails of the extended oligonucleotide, stating, for example, that "(i)mprovements to the speed and sensitivity of the assay for the extension product are achieved using such primers having tails." Davis (page 21) also states that because the complementary oligonucleotides may be synthesized inexpensively in great quantity and can therefore be applied to the substrate in great excess, the rate and amount of hybridization between the tail region of the extension product and the complementary immobilized oligonucleotide is increased.

Further, it is noted that while Applicants have relied on the teachings of Stryer to support their allegation of the disadvantages associated with using restriction enzyme digestion followed by electrophoresis and hybridization to detect a mutation, Stryer in fact teaches that this is an effective technique for detecting a point mutation. Stryer does not point to any insurmountable problems observed when performing hybridization of the "long-probe" to the restriction enzyme digested DNA. Rather, Stryer teaches the successful application of this technique to detect a mutation associated with single-cell anemia.

At page 13 of the response, Applicants state that Cohen specifically teaches the disadvantage of immobilizing a nucleic acid on a membrane in a Southern blotting technique. Applicants conclude that this teaching thereby teaches away from using the method of Davis which results in an immobilized nucleic acid. This argument is not persuasive because the teachings of Cohen relate to the immobilization of the target

nucleic acid irreversibly to the membrane in the method of Southern blotting. Cohen does not teach away from immobilizing a capture probe that is complementary to a tail region of the primer extension product.

At page 14 of the response, it is state that Cohen teaches "away from any technique which shared the requirement of immobilization on a membrane in either single-stranded or double-stranded hybrid form." However, there are no statements in Cohen which support such a conclusion. All teachings in Cohen regarding immobilization of nucleic acids are made in the context of methods in which hybridization between an immobilized nucleic acid and a second nucleic acid is performed under conditions in which the hybridization step itself distinguishes between nucleic acids that contain a single nucleotide mutation and nucleic acids that do not contain a single nucleotide mutation. The teachings of Cohen do not address the use of hybridization following the step which is performed to distinguish between nucleic acids having the mutation and nucleic acids not having the mutation. In particular, Cohen does not teach away from the method of Davis in which following primer hybridization and primer extension in solution, the primer extension product is immobilized in order to facilitate the separation of the primer extension product from the reaction components. As set forth by Davis, this methodology provides the advantage of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide. Thus, Davis specifically provides the motivation for combining the teachings set forth therein with the teachings of Cohen.

As stated in MPEP 2145:

"A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.)."

In the present situation, while Cohen teaches that methods which directly detect a point mutation by using an immobilized probe or target nucleic acid are inferior to methods which detect a point mutation using a primer extension assay, Cohen does not teach that the primer extension assay cannot be combined with an additional step in which the primer extension products are subsequently immobilized to facilitate their separation and detection.

Moreover, it is again pointed out that Davis and Cohen are analogous art since both the method of Davis and the method of Cohen rely on performing a primer extension reaction to detect a single nucleotide variation. On the other hand, Cohen and Southern do not rely on similar techniques to accomplish the detection of a single nucleotide variation, since Cohen teaches detecting a single nucleotide variation using a primer extension reaction and Southern teaches detecting a single nucleotide variation using a probe hybridization reaction.

For the reasons stated above, it is maintained that Cohen and Davis when considered as a whole would have lead the ordinary artisan to the claimed invention. As discussed in the above rejection, Davis teaches that the immobilization of primer extension products to a solid support via an affinity moiety allows for the use of multiple distinct primers simultaneously. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have used multiple primers, each having an affinity moiety and to have separated the primer extension products from the reaction medium by contacting the extension products with a solid support in order to have accomplished the objectives set forth by Davis of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

3. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO 90/11372, October 4, 1990; cited in the IDS) and Prober (U.S. Patent NO. 5,332,666).

The teachings of Cohen and Davis are presented above. The combined references do not teach using a terminator that comprises arabinoside triphosphate.

However, Prober teaches methods for determining a nucleotide sequence wherein the method comprises performing a primer extension reaction using a terminator. Prober teaches that the terminator may contain an arabinose as the sugar group and provides a number of examples of terminators comprising an arabinoside triphosphate (see column 18).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have a terminator comprising an arabinoside triphosphate because this would have provided an equally effective terminator for the extension reaction and for determining the identity of a nucleotide in a target nucleic acid.

RESPONSE TO ARGUMENTS:

In the response filed, Applicants traversed this rejection for the same reasons as set forth in paragraph 2 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

4. Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO 90/11372, October 4, 1990; cited in the IDS) and Tabor (U.S. Patent NO. 4,962,020; cited in the IDS).

The teachings of Cohen and Davis are presented above. The combined references do not teach including pyrophosphatase in the primer extension medium.

However, Tabor (columns 15-16) teaches including pyrophosphatase in primer extension reactions. The reference teaches that pyrophosphatase removes pyrophosphate which builds up during extension reactions. Specifically, Tabor (column 14) teaches that in the presence of pyrophosphate, DNA polymerase will add pyrophosphate to the 3' terminal nucleotide, causing the release of dideoxynucleoside

5'-triphosphates. As stated by Tabor (column 15, lines 1-2), "This reaction has the effect of removing the block at the 3' terminus."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Cohen so as to have included pyrophosphatase in the reaction medium in order to have achieved the expected benefit of eliminating pyrophosphorolysis activity of DNA polymerase and thereby reducing the probability that the labeled terminator would be removed and that unlabeled dideoxynucleotides would be released into the reaction medium. Thereby, the ordinary artisan would have been motivated to have include pyrophosphatase in the extension reaction in order to have ensured the accuracy and sensitivity of the method for determining the identity of a nucleotide.

RESPONSE TO ARGUMENTS:

In the response, Applicants traversed this rejection for the same reasons as set forth in paragraph 2 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Carla Myers

Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER